REMARKS/ARGUMENTS

Claim 8, as amended, is pending in the instant application.

I. Rejection under 35 U.S.C. § 103(a).

Claims 1-8 and 15-17 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,077,290. It was stated that ."...the only difference First, it should be pointed out that there are in fact **two** differences between the claimed compound and the compounds disclosed in US 5077290:

- The claimed compound (and all compounds originally claimed in the present application) has an **n-propyl** group on the morpholine nitrogen. Although the claims and broadest disclosure of US 5,077,290 may include a lower alkyl group on the morpholine nitrogen, the document does not contain any examples of a compound with an n-propyl group at this position – all of the specific compounds have a **branched** alkyl group on the morpholine N atom.
- The claimed compound has a methyl group at the 5-position of the morpholine ring. In contrast, in the compounds of US 5077290 the only substituent on a carbon atom of the morpholine ring is the heterocycle at the 2-position – as the general formula in the document clearly shows, the 3-, 5- and 6-positions are unsubstituted.

As supporting evidence, attached to this amendment is a declaration under 37 CFR § 132 by Dr Gillian Burgess, a senior director in Pfizer in the Sandwich Pain therapeutic area.

In the declaration Dr Burgess describes the results of a number of tests carried out on the claimed compound and the two enantiomers of Example 3 of US 5,077,290, which is considered to be the closest prior art compound. The results of the tests showed that the claimed compound demonstrated notably stronger activity at the D3 receptor in both a binding (using 2 different assay formats – one carried out internally, as described in Appendix 4 and Figure 1; the other external, as described in Appendices 1-3) and a functional assay (as described in Appendix 5 and Figure 2), than the more active enantiomer (enantiomer 1) of US 5,077,290, Example 3. Therefore, even stronger activity for Example 67 would be projected as compared to the racemic mixture as

disclosed in US 5,077,290, Example 3.

It is a general principle in the field of drug discovery that compounds of higher potency (binding and functional activity) are expected to elicit *in vivo* effects at lower unbound plasma concentrations with potential for a lower human dose size and reduced risk of adverse side effects. Therefore, given its enhanced potency at the D3 receptor, the claimed compound would be expected to elicit a response at a lower dose and/or at unbound drug levels in the clinic than enantiomer 1 of Merck Example 3 or, most particularly, the racemic mixture as disclosed in US 5077290.

Furthermore, it is a commonly encountered feature of structure-activity relationships in the field of medicinal chemistry that small structural changes can have profound and unpredictable effects on biological activity, either advantageous or deleterious (several examples are described in: *Specific Substituent Effects*. C.G. Wermuth, Ed. Wermuth, C.G. Practice of Medicinal Chemistry (1996), 312-344. Publisher: Academic, Pub. London, UK – attached as Reference 1 to the declaration).

In particular, it is widely known that biological and pharmacological activity is often highly dependent upon stereochemistry. Several relevant examples are described in the review article *Stereoselectivity in drug action and disposition: an overview.* Patel, B. K.; Hutt, A. J. Ed. Reddy, I. K.; Mehvar, Reza. in: *Chirality in Drug Design and Development* **2004**, 139-190. Pub. Marcel Dekker, Inc., New York, N.Y – attached as Reference 2. Appreciation of stereochemical issues in drug design and development have increased in the last few decades, such that it is now deemed good practice, and a requirement of many pharmaceutical regulatory authorities, to develop chiral drugs as single enantiomers (and stereoisomers).

With particular relevance to this case, the structural changes and specific stereochemistry required to increase potency at the D3 receptor afforded by example 67 as compared with U.S. 5,077.290 Example 3, could not have been predicted and were not suggested by the prior art.

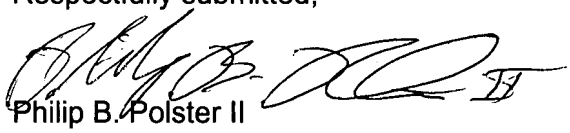
II. Request for Continued Examination (RCE)

The present Office Action has been made Final. The Applicants have included an RCE in the present Office Action response.

III. Conclusion

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, the Examiner is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,



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